16. MULTIPLE MALFORMATIONS (N)

When there is abnormal development of one part of the body some significant deviation from normal morphogenesis elsewhere is probably the rule rather than the exception. The proportion of cases in which this phenomenon is demonstrated depends on the thoroughness of clinical examination, the period of time over which the patient is observed and the numbers of patients who die and are examined at autopsy. Pleiotropic defects of single-gene mutations are well known and indeed are so common that most geneticists tacitly assume that failure to demonstrate more than one characteristic phenotypic expression of a gene merely represents failure of observation or of opportunity to observe or lack of an appropriate technique.

Not surprisingly the same situation holds when any genotypic contribution to etiology is complex and multigenic. If a purely environmental explanation for abnormal development is postulated, in view of the action of noxious agents acting on the embryo having a time specificity which on occasion seems more important than that of the nature of the teratogenic agent, the same phenomenon of more than one defect in the same child would be expected. If, as seems a reasonable working hypothesis, developing tissues are most susceptible to deviant growth when cell division and functional differentiation of cells are proceeding rapidly, then any time factor of action of a teratogenic agent or failure of a particular gene activity in development might be expected to be reflected in anomalous growth in widely separated tissues and organs. Alternatively, if the intra-uterine environment is unfavourable in respect of factors influencing normal morphogenesis over a long period of time the same results—developmental errors in widely separated structures—would be anticipated.

It has been a valid criticism of most published papers concerned with series of cases of congenital malformations that there have been included many only described as " multiple ". That authors should leave themselves open to such criticism is entirely understandable. Editors of journals are reluctant to give the amount of space necessary to set out in print the details of combinations of malformations in many infants. Perhaps even more important, it is a formidable problem for any author to assemble a sufficient body of data in respect of a large number of these cases of malformations where autopsy has revealed most of the obvious abnormalities. Inevitably he feels that it is not justifiable to press an editor for presentation of data on which he cannot comment with any degree of clarity or conviction. Even if a large amount of data is available there are many problems of analysis and presentation of such information in any compact form. Possibly there has not been any clearly formulated idea as to what is of interest or value in such data and therefore there have not been any strongly held views as to why they should be analysed.

It seems to the present authors that there are several reasons why analyses should be attempted although an elaborate specialized consideration of the present data would completely upset the balance of this report. There appear to be two outstanding reasons for a detailed analysis:

(*a*) Only extensive study of large bodies of data permits of identification of recurring syndromes and recurring associations. Apart from the genetic interest, identification of such syndromes and associations would suggest, in environmental terms, the effect of noxious agents exerting their influences *in utero* early in pregnancy. The examples of the teratogenic actions of rubella virus and thalidomide spring to mind, but taken in association with any suggestion of geographic, ethnic, or socio-economic variations, however laborious such an extensive study may be, it would be expected in time to yield dividends in terms of identification of specific etiological factors and possibly open the way to exhibition of preventive measures.

(*b*) The second reason would be to test, however crudely, hypotheses that time-specificity was, on the whole, more marked than agent-specificity or that the agent or agents acted on short or long periods of embryogenesis. An identification of groupings of malformations could in a crude way be considered as possibly representing *post hoc* evidence either of the times of action of gene mutations in embryogenesis or of a noxious influence exerting its effect over either a short time or a considerable period of embryogenesis. Evaluation of data would require an allocation to time or origin of each effect. This is by

no means easy and certainly most embryological textbooks are not written in such a way as to allow relevant information, however crude, to be derived.

If opinions could be formed on the basis of this approach, again it would serve, as in a detective story, to " narrow the list of suspects ".

APPROACHES TO SETTING OUT AN ANALYSIS OF DATA RELATING TO MULTIPLE MALFORMATIONS

Most writers have contented themselves with taking arbitrarily a particular malformation, or group, and then considering the range of other malformations found associated. Thus, it might be considered that anencephalus or harelip and/or cleft palate was in some way the principal malformation or one most consistently recognized, whether or not there were others in the same child. This is the practice which has been followed in various preceding sections. However, such an approach tends to result in neglect of any less dramatic abnormalities not occurring in association with the major malformations as the association of two or more lesser anomalies would not be considered. From data so presented the question whether two or more lesser anomalies occur together independently of association with the " dramatic " abnormality cannot be examined.

Ideally we might start with the frequency of occurrence of pairs of any two abnormalities (defined with as great precision as possible), whether they occurred in the form of only two abnormalities in the same child or as two of a greater number. Such information could easily be presented in a two-way table by sex. By extension we might examine whether these two were more commonly found together in association with a third, and so on. The logic of such an approach must result in a tremendous amount of computing and applications of advanced statistical methods to the analysis.

THE PRESENT DATA ON MULTIPLE MALFORMATIONS IN THE N GROUP

Ignoring multiple malformations in cases of Down's syndrome (A), in neural tube defects (B1-B7), in the syndromes affecting only one system (for example in the E, K and L groups), and in specific well-known syndromes in the M group, there were left 329 cases in single births which were placed in the N group.

The entire information available to the writers is set out in the Basic Tabulations by Centres booklet. Of these 329 cases, 49 were stillborn, 138 died in hospital, and 142 were liveborn and left hospital alive; 195 were males, 122 were females, and in 12 the sex was indeterminate. It was known whether or not an autopsy had been performed in 160 of these, and 102 had in fact been so examined.

Data in respect of multiple malformations in which some specific anomalies occurred have been discussed in several of the preceding sections. In particular the associations of harelip with or without cleft palate and isolated palates have been considered in section 9, those of the various defects of the intestinal tract in section 7, those associated with malformations of limbs and extremities in section 12, and some of those associated with miscellaneous defects, in particular malformations of the ear, in section 15.

In a brief account such as this the data are perhaps best presented in such groups of cases, the grouping being determined by arbitrary choice of a readily recognizable and definable malformation although this leads to difficulties when, as is inevitable, two chosen malformations occur in the same child, for example, harelip and cleft palate, and exomphalos or tracheo-oesophageal fistula and atresia of anus. In such cases the same case has to appear in two or more tabulated groupings.

For ready reference the individual malformations which appear to occur most frequently as one of a series of malformations in each child and the percentage of the N-group cases in which they occur are listed in Table 16.1. Perhaps the most remarkable feature of this table is the high proportion of all multiple malformations which include one or more of anomalies of the urogenital tract, cardiac malformations, exomphalos or agenesis of the abdominal wall, harelip and/or cleft palate, cleft palate alone, talipes (although see observations about diagnosis in section 10), and malformations of the extremities and abnormalities of ears. Even if these anomalies in Table 16.1 occur in the same child they are listed separately, so that the total of cases is, in fact, greater than all the cases in the N group.

It is hoped to publish at a later date an analysis of these multiple abnormalities and to compare them with data accumulated in other investigations.

TABLE 16.1

NUMBERS OF CERTAIN DEFECTS OCCURRING IN THE 329 CASES IN THE N GROUP

Cases where one of the malformations was:	Number of cases				
	M	F	? Sex	T	%[a]
Malformations of heart and great vessels	41	32	0	73	22.2
Tracheo-oesophageal fistula/oesophageal atresia	8	7	0	15	4.5
Atresia ani (excluding cases of sirenomelia)	26	10	3	39	9.9
Other stenoses of gut	6	4	0	10	3.0
Exomphalos (including agenesis of abdominal wall)	17	13	3	33	10.0
Diaphragm defect	4	6	0	10	3.0
Harelip	7	2	1	10	3.0
Harelip and cleft palate	36	10	0	46	14.0
Cleft palate	18	19	0	37	11.2
Talipes	32	19	1	52	15.8
Polydactyly (ulnar) or (NFS) of hands	16	9	0	25	7.6
Polydactyly of hands and feet	5	0	0	5	1.5
Polydactyly (radial) (bifid thumb)	4	2	0	6	1.8
Syndactyly	5	5	0	10	3.0
Other digital anomalies	8	7	0	15	4.5
Reduction deformities	3	5	0	8	2.4
Other limb anomalies	18	10	1	29	8.8
All urogenital anomalies	69	24	9	102	31.0
Anophthalmia or microphthalmia	9	11	0	20	6.1
Abnormal ears	19	21	0	40	12.1
Atresia of external auditory meatuses	5	6	0	11	3.3

[a] Percentage of total cases in N group where specified anomaly occurred.